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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/581,274	05/30/2008	David John Grainger	0783-01-002US1	1913

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EXAMINER	
VAKILI, ZOHREH	
ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
07/11/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@virtuallawpartners.com

Office Action Summary	Application No.	Applicant(s)	
	10/581,274	GRAINGER ET AL.	
	Examiner	Art Unit	
	ZOHREH VAKILI	1629	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 December 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/22/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 3-29 are presented for examination.

Applicant's Amendment filed 12/22/2010 has been received and entered into the present application. Claims 3-29 are pending and are herein examined on the merits.

Applicant's arguments, filed 12/22/2010 have been fully considered. Rejections not reiterated from previous Office Actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set of rejections presently being applied to the instant application.

Claim Rejections - 35 USC § 112 (New Matter)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 5 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant adds new limitations to the claims that raise the issue of new matter. New matter issues are raised when Applicant includes limitations

in the claims that he/she clearly did not have possession of at the time of invention. The silence of the disclosure regarding other than *ter*-butyloxy is not sufficient to now claim the exclusion of such steps because nowhere in the disclosure has Applicant discussed alkoxy other than *ter*-butyloxy in the context of the claimed composition.

Claim Rejections - 35 USC § 112

> The following is a quotation of the second paragraph of 35 U.S.C. 112:
>
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3, 20, 27, and 29 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

These claims contain parenthetical information which renders the claims vague and indefinite. It is not clear if the information provided within the parentheses should be interpreted as claim limitations. Further, when a claim recites “for example” it is not clear what else can be included and what more information is actually missing from the body of the claims. Therefore, it is not clear are these information limitations to be included or to be excluded from the interpretation of the subject matter of the claims.

Claim Rejections - 35 USC § 112 Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3, 4, and 7-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for some assays determining the anti-inflammatory activity of the compounds does not reasonably provide enablement for all the pharmaceutical composition and methods of treating osteoprosis, asthma, Alzheimer's disease, organ transplant rejection, viral infection, skin wounds, autoimmune disease, tumor growth, and many others (see claim 19). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Following reasons apply:

Scope of Enablement

To be enabling, the specification of the patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification

in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).1[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,
6) the relative skill of those in the art,
7) the predictability of the art, and
8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. In re Fisher, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative

Skill level

The invention relates to a pharmaceutical composition and method of treating inflammatory disease such as tumor growth, which reads on cancer. The relative skill of those in the art is high, that of an MD or PHD. That factor is outweighed, however, by the unpredictable nature of the art. As illustrative of the state of the art, the examiner cites for the treatment of cancer as an example, Voskoglou-Nomikos et al., Clinical Cancer Research, Vol. 9, pp. 4227-4239, Sept. 12, 2003. (a copy enclosed with this action). The reference relates to unpredictability of treating cancers/tumors of different types. The reference teaches the relative merits of cell culture, human xenograft and mouse allograft preclinical cancer models. See the entire document especially the results. On page 4227. The reference teaches that predicting the activity of a compound for treating various typre of cancers is not possible, See the entire document especially page 4237 which is as follows:

The NCI work with cancer drug screening programs from 1955 to 1990 (Refs. 5–8, 10–12; leukemia-based preclinical, compound-oriented screens preferentially yielding compounds active against hematological malignancies) in combination with our work and recent conclusions by Johnson *et al.* (Ref. 18; statistically significant results under the compound-oriented approach for some solid tumors) suggest that the compound-oriented strategy may be successful when used only within solid tumors or only within hematological malignancies but not when the two disease groups are considered together.

In general, our results suggest that the *in vitro* human tumor cell line and the human xenograft models might have good clinical predictive value in some solid tumors (such as ovary and NSCLC) under both the disease and compound-oriented strategies, as long as an appropriate panel of tumors is used in preclinical testing.

In conclusion, given the results in this study and those of others (6, 7, 10–12), continued use of the murine allograft model in drug development may not be justified. The work presented here argues for emphasis to be placed on *in vitro* cell lines (in the context of the NCI Human Tumor Cell Line Screen) and appropriate panels of the human xenograft model.

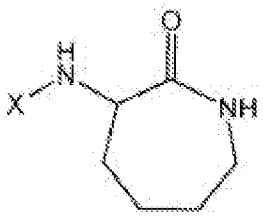
Recent years have seen an explosion in the molecular understanding of cancer, which has led to the development of not only more effective cytotoxic cancer drugs but of potentially cytostatic or antimetastatic agents as well. The future preclinical and clinical development of traditional cytotoxic compounds will likely follow similar procedures with those practiced today, and in that sense, the present findings could contribute to the more efficient discovery of such agents. However, the existing cancer models and parameters of activity in both the preclinical and clinical settings may have to be redesigned to fit the mode of action of the novel cytostatic, antimetastatic, antiangiogenesis, or immune response-modulating agents (58). In the preclinical cancer model front, the case is being made for the use of the orthotopic mouse xenograft and transgenic models (59–61) because those are thought to more accurately simulate human disease, especially in terms of growth characteristics and metastatic behavior. New end points of preclinical activity are contemplated such as the demonstration that a new molecule truly hits the intended molecular target (58). In Phase II clinical trials, there is a growing effort toward validating new surrogate endpoints of drug efficacy (58). The next decade will probably answer many of the questions regarding the effectiveness of these novel agents and will likely define a new role for tradi-

tional cytotoxic therapies, but it will also bring new challenges in terms of preclinical predictors of activity.

The reference teaches about the unpredictability to treat cancers.

2. The amount of direction or guidance provided and the presence or absence of working examples

The presently claimed invention is directed to a pharmaceutical composition comprising, as an active ingredient a compound of formula I in the treatment of autoimmune diseases, vascular disorders, viral infection or replication, asthma, osteoporosis (low bone mineral density), tumor growth, rheumatoid arthritis, organ transplant rejection and/or delayed graft or organ function, a disorder characterized by an elevated TNF-(x level, psoriasis, skin wounds, disorders caused by intracellular parasites, allergies, Alzheimer's disease, antigen induced recall response, immune response suppression, multiple sclerosis, ALS, fibrosis, and formation of adhesions.



(I)

Compound formula I represented above wherein X is -CO-R1 or -SO2-R2, R1 is an alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl or alkylamino radical of 4 to 20 carbon atoms (for example of 5 to 20 carbon atoms, of 8 to 20 carbon atoms, of 9 to 20 carbon atoms, of 10 to 18 carbon atoms, of 12 to 18 carbon atoms, of 13 to 18 carbon atoms, of 14 to 18 carbon atoms, of 13 to 17 carbon atoms, with the proviso that R1 is not 5-methylheptanyl or 6-methylheptanyl where the R1 radical is linked to the carbonvl

at its 1-position; and R2 is an alkyl radical of 4 to 20 carbon atoms (for example of 5 to 20 carbon atoms, of 8 to 20 carbon atoms, of 9 to 20 carbon atoms, of 10 to 18 carbon atoms, of 12 to 18 carbon atoms, of 13 to 18 carbon atoms, of 14 to 18 carbon atoms, and of 13 to 17 carbon atoms); or alternatively R1 and R2 may be selected independently from a peptido radical having from 1 to 4 peptidic moieties linked together by peptide bonds (for example a peptido radical of 1 to 4 amino acid residues).

In order to achieve the claimed therapeutic objective of treating autoimmune diseases, vascular disorders, viral infection or replication, asthma, osteoporosis (low bone mineral density), tumor growth, rheumatoid arthritis, organ transplant rejection and/or delayed graft or organ function, a disorder characterized by an elevated TNF-(x level, psoriasis, skin wounds, disorders caused by intracellular parasites, allergies, Alzheimer's disease, antigen induced recall response, immune response suppression, multiple sclerosis, ALS, fibrosis, and formation of adhesions. There are myriad variants of compounds and diseases. Which compound is going to treat which disease. However, the instant specification as originally filed lacks adequate guidance, direction or discussion to apprise the skilled artisan of the specific conditions and/or starting materials and/or reaction schema to be used to synthesize the claimed compounds of the general formula. In the absence of such direction or guidance, the instant specification fails to provide adequate enabling disclosure to practice the full scope of the claimed subject matter.

The protective groups can be introduced and eliminated according to conventional methods used in organic synthetic chemistry. In such processes, if the

defined groups change under the conditions of the working method or are not appropriate for carrying out the method, the desired compound can be obtained by using the methods for introducing and eliminating protective groups which are conventionally used in organic synthetic chemistry. Conversion of functional groups contained in the substituents can be carried out by known methods. In addition to the above-described processes, and some of the active compounds of formula I may be utilized as intermediates for further synthesizing novel derivatives according to formula I."

The specification provides no direction or guidance for practicing the claimed invention in its "full scope". No reasonably specific guidance is provided concerning useful therapeutic protocols for the claimed methods. The state of the art clearly shows that prediction of the treatment or using the compounds of claim 3 is not possible one skilled in the art would have to go through undue experimentation to use the claimed invention.

There are some assays disclosed in the specification such as described on page 52, *Test protocol*. Present disclosure does not teach the treatment of any cancer or any other diseases mentioned in claim 19. There is no guidance or teaching how modulating metastasis of cancer will be treated or Alzheimer's disease or immune response suppression, or many other diseases as mentioned in claim 19. The instant disclosure provides no evidence to suggest that this activity can be extrapolated to all type of cancers and various diseases as claimed in claim 19 having unrelated mechanisms, and thus does not meet the "how to use" prong of 35 USC 112, first

paragraph. The state of pharmaceutical art is unpredictable. It requires each embodiment to be individually assessed for physiological activity. See in re Fischer, 427 F 27 2d. 833, 166 USPQ 18 (CCPA) 1970) where it indicates that the more unpredictable the treatment is the more specific enablement is needed in order to satisfy the statue.

The treatment of cancer and other diseases as claimed is highly unpredictable because of the complexity of the human body and the differences in the underlining causes of the vast array of conditions encompassed by the instant invention. There is a lack of showing in the medical art of utilization of a single agent or a group of agents with closes structural similarity in the treatment of all the disorders encompassed by the claimed invention. The state of the art shows the treatment of cancers by even one compound. (see the reference cited above). The skilled artisan would have definitely doubt about the claimed compounds would be effective in treating all the cancers and other diseases or conditions encompassed by the claimed invention.

3. The quantity of experimentation necessary

Because of the known unpredictability of the art, and in the absence of experimental evidence, no one skilled in the art would accept the assertion that the instantly claimed agents could be predictably used for treating cancers and various other diseases as inferred by the claim and contemplated by the specification. In absence of showing correlation between all the conditions and cancers encompassed by the present claims and effectiveness of the claimed compounds in treating, one skilled in the art would be unable to fully predict the effect and activity of the compounds

after the administration. Only guidance present in the specification is the assays. In order to practice the invention commensurate in scope with the instant claims, one skilled in the art would have to go through undue experimentation to determine the conditions treatable by the claimed compounds with no assurance of success.

Accordingly, the instant claims do not comply with the enablement requirement of §112, to practice the claimed invention in its "full scope" a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

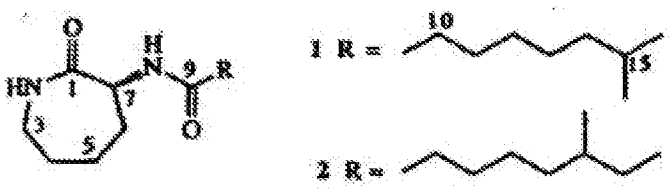
Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 5, 6, and 27-29 are rejected under 35 U.S.C. 102(b) as being anticipated by Davidson et al. "Isolation and Synthesis of Caprolactins A and B, New Caprolactams from a Marine Bacterium; 1993; Tetrahedron, Vol. 49, no. 30, pp. 6569" (cited on IDS).

Davidson et al. disclose the general formula of compound I, reproduced below, (see pp. 6569).



Consequently, the reference anticipates the claimed invention defined in claims 5, 6, and 27-29.

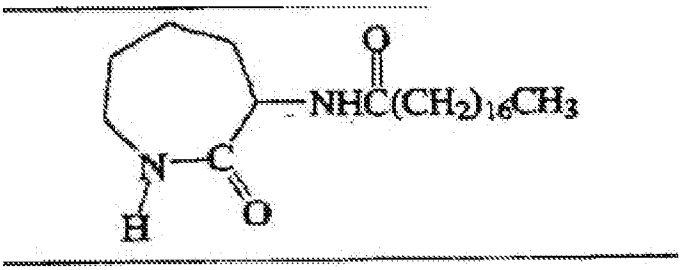
Claim Rejection - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 5, 6, and 27-29 are rejected under 35 U.S.C. 102(a) as being anticipated by JP 2003-145933 (cited on IDS)

JP 2003-145933 discloses the general formula of compound I, reproduced below, see pp. 6, compound 13.



Consequently, the reference anticipates the claimed invention defined in claims 5, 6, and 27-29.

Conclusion

No claims of the present application are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zohreh Vakili whose telephone number is 571-272-3099. The examiner can normally be reached on 8:30-5:00 Mon.-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Lundgren can be reached on 571-272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Zohreh Vakili

Patent Examiner May 19, 2011
Art Unit 1629

/Jeffrey S. Lundgren/
Supervisory Patent Examiner, Art Unit 1629